Curr Infect Dis Rep (2017) 19: 1
DOI 10.1007/s11908-017-0556-y

NMDAR Encephalitis Following Herpes Simplex Virus Encephalitis

Jonathan Galli[1] · **Stacey L. Clardy**[1] · **Amanda L. Piquet**[1]

Published online: 19 January 2017

Abstract
Purpose of Review Herpes simplex virus encephalitis (HSVE) is often associated with significant morbidity and mortality, and despite appropriate treatment with antivirals, worsening of neurological symptoms or relapse occurs in a subset of patients. Recent data suggests that many relapses are likely caused by a secondary immune response, with the N-methyl-D-aspartate receptor (NMDAR) antibody being the most commonly associated autoantibody. We provide a review of the relevant literature, examining the relationship between HSVE and development of autoimmunity.
Recent Findings Autoantibodies, including pathogenic NMDAR antibody, have been demonstrated in the cerebrospinal fluid (CSF) of patients following HSVE. This occurs usually several weeks following initial HSV infection.
Summary There is growing evidence of a relationship between HSVE and the subsequent development of NMDAR encephalitis. Possible mechanisms include molecular mimicry or an immune response to direct neuronal damage. Future studies should address if the use of immunotherapy can prevent the development of autoimmunity following HSVE.

Keywords N-methyl-D-aspartate receptor (NMDAR) antibody · Herpes simplex virus · Encephalitis · Autoimmune · Cell surface antibody

This article is part of the Topical Collection on *Neurological Infections*

✉ Amanda L. Piquet
Amanda.piquet@hsc.utah.edu

[1] Department of Neurology, University of Utah, Salt Lake City, UT, USA

Introduction

Encephalitis is commonly encountered in neurology with significant associated morbidity and mortality. Often associated with viral or autoimmune etiologies, a clear causative agent is not determined in over half of cases despite extensive evaluation [1•]. Multiple viruses can cause encephalitis, but herpes simplex virus (HSV) is the most commonly encountered virus in developed countries. Herpes simplex virus encephalitis (HSVE) causes a monophasic disease course that most commonly presents clinically with fever, altered mental status, and seizures. Viral encephalitis is a neurological emergency requiring prompt diagnosis via cerebrospinal fluid (CSF) nucleic acid, serological testing, or antigen detection [2]. CSF examination most often demonstrates a lymphocytic pleocytosis with a positive HSV—polymerase chain reaction (PCR) being diagnostic. Magnetic resonance imaging (MRI) can demonstrate temporal lobe changes [3]. Treatment with antiviral medication, specifically in the setting of HSVE, has been demonstrated to improve survival in adults and is therefore empirically started prior to diagnosis when viral encephalitis is suspected [2, 4].

Antibodies targeted against specific neural antigens are increasingly recognized as a common etiology of encephalitis. While autoimmune encephalitis was previously thought to be a rare entity, evidence from the California Encephalitis Project has demonstrated that in patients younger than 30 years old, the frequency of N-methyl-D-aspartate receptor (NMDAR) encephalitis exceeds that of viral encephalitis in the USA, emphasizing the importance of early consideration of autoimmune encephalitis to ensure prompt and appropriate diagnosis and treatment [5]. Beyond just NMDAR encephalitis, other antibodies against cell surface and synaptic antigens are being identified with increasing frequency, including autoantibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic

acid receptor (AMPAR), γ-amino-butyric acid B-receptor (GABA-BR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like (CASPR2), metabotropic glutamate receptor 5 (mGluR5), dipeptidyl-peptidase-like protein-6 (DPPX), immunoglobulin-like family member 5 (IgLON5), and glycine receptor (Gly-R) antibodies [6–9]. With the evolving field of neuroimmunology, new autoantigens continue to be discovered. In contrast to the classical paraneoplastic neurological disorders—which are usually associated with intracellular antibodies resulting in often irreversible central nervous system damage—autoimmune encephalitis with antibodies against cell surface and synaptic antigens are associated with extracellular epitopes which undergo a reversible disruption of structure or function which is often responsive to immunotherapy [10, 11]. The clinical syndrome of NMDAR encephalitis is the most studied and well-characterized, generally with a clearly recognized progression from psychosis and behavioral changes to seizure and movement disorders and often to autonomic instability, hypoventilation, and even coma [12]. Cell surface antibody-associated encephalitis can—but does not always—demonstrate associated electroencephalogram (EEG) and MRI changes in the temporal lobes, as well as abnormal CSF studies with pleocytosis, elevated protein, presence of oligoclonal bands, and/or demonstration of the associated antineuronal antibody in the CSF [13]. Frequently, EEG does not demonstrate frank epileptiform discharges and may only demonstrate intermittent rhythmic delta activity and/or slowing of background activity [13, 14]. Treatment with tumor removal, if present, and immunotherapy with steroids, intravenous immunoglobulin, and/or plasmapheresis is effective in a majority of patients. Second-line immunotherapy with either rituximab and/or cyclophosphamide can be effective in those refractory to first-line therapy [12]. The different neuronal antibodies are predictive of different types and rates of underlying malignancy, and thus ongoing malignancy screening is often recommended in a subset of patients, depending on the clinical context.

Differentiating between infectious and autoimmune etiologies can be challenging; however, there are characteristic clinical and laboratory findings that can help to clarify the diagnosis. EEG and MRI can also be useful in elucidating a diagnosis, with HSVE more often demonstrating extensive frontal and/or temporal lobe changes in comparison to NMDAR encephalitis [1•, 3].When patients present with more ambiguous symptoms, however, delay in diagnosis can occur while relying on time-consuming testing. Additionally, there is likely a complex relationship between infectious and autoimmune encephalitis, and recently, an association between HSVE and development of autoimmune encephalitis has been suggested [15•]. Here, we provide a review of recent literature which examines HSVE and its involvement in the development autoimmunity, and we also discuss the relationship and possible mechanisms of autoimmunity following HSVE, and the potential therapeutic implications.

Clinical Presentation

HSVE typically follows a monophasic course, but relapses have been reported despite appropriate treatment with acyclovir [16]. Historically, as many as 10–25% of patients experienced recurrence of neurological symptoms [17, 18], but in most cases of presumed relapse, there has been an inability to detect replicating virus in brain tissue or viral DNA in the CSF [17]. It has been suggested more recently that a subgroup of the patients who clinically worsen following treatment for HSVE may secondarily develop antibodies against NMDAR, manifesting a distinct, post-infectious autoimmune encephalitis. This has been demonstrated in patients with post-HSVE with recurrent symptoms (commonly movement disorders in children and psychiatric symptoms in adults) occurring about 4 to 6 weeks following HSVE infection, serum, and CSF studies negative for infectious etiology, new confluent white matter signal abnormality in repeat imaging, and clinical improvement after immunotherapy [19•, 20, 21]. Figure 1 demonstrates MRI findings seen in a 12-month-old girl with positive NMDAR antibodies in the CSF that developed several weeks after acute infectious encephalitis with HSV-1.

The development of NMDAR autoantibodies as well other, often unclassified, neuronal autoantibodies in the setting of HSV central nervous infection supports the idea that HSVE can act as a trigger for autoimmunity [22•]. Several mechanisms have been suggested which may explain the parainfectious development of autoantibodies in relation to HSVE, including molecular mimicry and/or antigen exposure in a primed milieu secondary to the neuronal tissue damage and inflammation from the virus [15•].

Evidence of HSVE-Induced Autoimmunity

The presence of NMDAR antibodies occurring in patients with HSVE was examined by one study in 2012 using archived serum and CSF that tested from a total of 44 patients with HSV-PCR positivity and otherwise clinical presentations consistent with HSVE [19•]. The serum and CSF of these patients were retrospectively analyzed for the presence of neuronal antibodies, with particular attention to NMDAR antibodies—the specific antibody associated with the disorder is IgG antibodies against the NR1 subunit of the NMDAR [23]. The authors detected a total of 13 out of 44 patients with the presence of NMDAR antibodies [19•]. Antibody subclasses were further divided into five patients with IgG, nine with IgA, and nine with IgM. All patients with NMDAR antibodies demonstrated activity at either the NR1a subunit alone or concomitant activity against the NR1a and NR2b subunits, with identical immunofluorescence patterns demonstrated with both. All classes of antibodies demonstrated a pathogenic reduction in the expression of synapsin, a synaptic marker, in

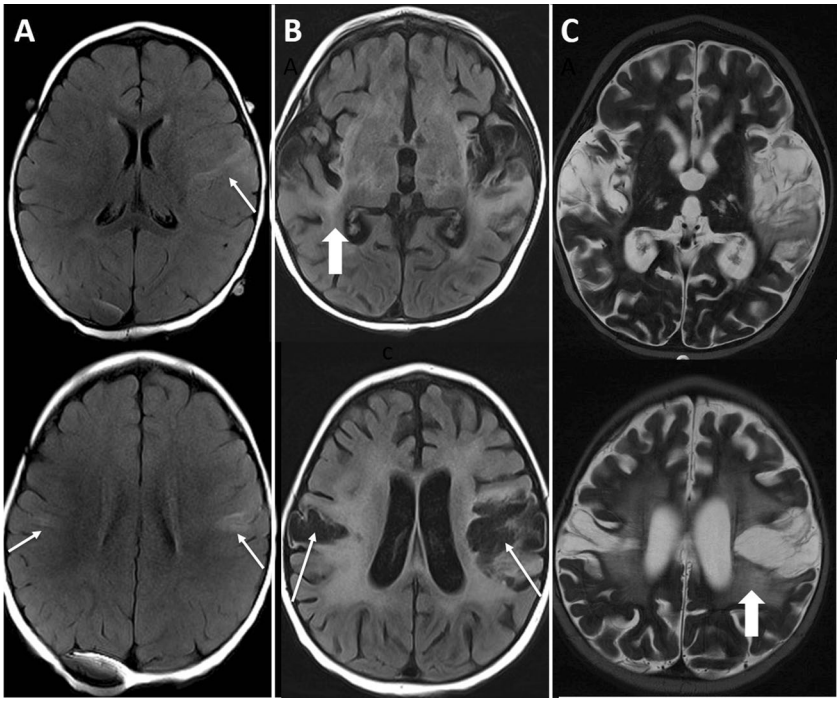

Fig. 1 MRI of a 12-month-old girl with post-HSVE NMDAR encephalitis. **a** Fluid-attenuated inversion-recovery (FLAIR) sequences within 48 h of symptom onset of fever and seizures; herpes simplex virus-1 polymerase chain reaction (HSV-PCR) was positive in the CSF. There are T2 hyperintensities involving the perirolandic regions (*thin arrows*). **b**, **c** FLAIR sequences and T2 sequences, respectfully, 15 weeks after her initial presentation. These sequences show significant encephalomalacia in the region of the original abnormalities (*thin arrows*) as well as confluent white matter signal distinct from the original lesions have occurred (*thick arrows*). Additionally, there is global atrophy noted compared to the original study

hippocampal neuronal cultures, thus suggesting that all the Ig classes against NMDAR could be pathogenic [19•]. They found no difference in the clinical presentation of patients with NMDAR antibodies in comparison to those without detected NMDAR antibodies, and while they appropriately concluded that the presence of NMDAR antibodies alone is not equivalent to NMDAR encephalitis, they clearly demonstrated the presence of a pathogenic NMDAR antibody targeting the NR1a subunit occurring in the setting of HSVE [19•].

Further evidence of an association between HSVE and the presence of NMDAR antibodies was demonstrated in 2013 in a pediatric patient with post-HSVE choreoathetosis who demonstrated serum and CSF NMDAR IgG antibodies and experienced clinical improvement following immunotherapy [20]. While the synthesis of the NMDAR antibody in relation to the diagnosis of herpes encephalitis was unclear in this patient as the samples were examined retrospectively, an analogous observation of an adult patient demonstrated the absence of NMDAR antibodies at presentation of HSVE, but subsequent detection during relapsing relapse of neurologic symptoms in the absence of HSV nucleic acid detection [24]. These single-case observations supported the idea that HSVE may contribute to autoimmunity against synaptic receptors in the setting of subsequent generation of NMDAR antibodies.

In 2014, a study of patients with relapsing post-HSVE at the University of Barcelona prospectively identified five patients (four children and one adult) who presented with neurological relapse with positive NMDAR antibodies identified [15•]. Relapse occurred at a median of 24 days, with the pediatric patients demonstrating choreoathetosis and mental status changes and the adult patient demonstrating abnormal behavior and personality. There was no clinical or laboratory evidence of HSVE recurrence; however, each of the five patients was found to have NMDAR antibody positivity 3–5 weeks following initial disease course, which were not present during the initial HSVE infection. Apart from one patient who improved spontaneously, the other four patients experienced improvement after a course of immunotherapy. In addition, 34 patients with definite or probable HSVE were included to determine the frequency of neuronal antibodies after infection. The authors also retrospectively studied the archived serum and CSF of 34 patients following HSVE. Antibodies in the serum and CSF developed in 1/17 and 5/22 patients, respectively, during the first week of HSVE and developed in 5/13 and 7/12 patients, respectively, following HSVE. Of the 12 patients that developed antibodies to neuronal antigens, two developed NMDAR antibodies, nine developed antibodies against unknown antigens, and one

developed antibodies to both the NMDAR and unknown antigens. These retrospective findings suggest that the presence of autoantibodies increased over time following infection with HSVE and that the initial HSV infection may lead to release of multiple antigens which can serve as potential targets for development of autoimmunity against various antigenic targets [15•]. Thus, supporting the theory that NMDAR antibodies can develop in association with HSVE.

Possible Mechanisms

There is growing evidence supporting the relationship between HSVE and the subsequent development of neurologic autoimmunity, but the mechanism of development of this neuronal autoimmunity following HSV infection has not yet been clearly demonstrated. A candidate mechanism is molecular mimicry—similar to the commonly proposed theory for cases of autoimmune encephalitis that occur without obvious infectious or neoplastic trigger. This theory has been historically posited for other autoimmune neurologic conditions, including immune-mediated demyelination of peripheral nerves in the setting of C*ampylobacter jejuni*, as seen in Guillain-Barre syndrome, and Sydenham chorea secondary to *Streptococcus pyogenes* infection [25, 26]. Other viral infections, including the human T cell lymphotropic virus type 1 (HTLV-1) and Epstein-Barr virus (EBV), have been implicated as potential generators of autoimmunity more broadly in central nervous system disease. Support for the mechanism of the chronic neurological deficits caused by HTLV-1, for example, is the cross-reaction between the Tax protein (an oncoprotein causing dysregulation of the cell cycle) on the virus and the intracellular neuronal protein (neuronal self-antigen heterogeneous nuclear ribonucleic protein-A1, or hnRNP-A1), allowing for antibody-mediated glial damage [27]. Evidence of cross-reactivity between EBV and myelin basic protein as a possible mechanism for the central nervous system demyelination occurring in multiple sclerosis has long been studied as a potential mechanism whereby viral infection can possibly lead to neurological disease via molecular mimicry [28]. While it is plausible to suggest a similar cross-reactivity with the HSV leading to the development of NMDAR antibodies, no epitope on the virus has been identified as a possible culprit. Furthermore, the discovery of multiple autoantibodies in relation to HSVE argues that molecular mimicry alone does not suffice as a mechanism explaining entire immunological response occurring following HSVE [15•].

Another mechanism could involve the sequelae of a robust immune system response to the damage from the HSV infection, leading to the development of autoimmunity against the otherwise normally unexposed neuronal antigens. The concomitant presence of antibodies targeting neuronal antigens and the presence of the herpes virus is not isolated to the HSV, but has also been demonstrated with EBV, varicella zoster virus (VZV), and human herpesvirus 6 (HHV-6) [22•]. Additionally, the development of relapsing symptoms like that observed with NMDAR encephalitis has been demonstrated in patients with VZV [29, 30]. This suggests that the immune response leading to the development of NMDAR autoantibodies and subsequent development of NMDAR encephalitis is not due to the presence of the HSV specifically, but rather the immune response and development of synaptic autoimmunity may be secondary to the inflammation and neuronal tissue damage. This is further evidenced by the demonstration of autoantibodies against other neuronal antigens—not exclusively against NMDAR—following HSVE [15•]. With HSVE often affecting limbic structures, which have a rich expression of NMDA receptors, it is possible that the inflammation and damage leading to subsequent release of otherwise immune privileged NMDAR and other neuronal antigens can induce a broad autoimmune response to these potential epitopes. This anatomic affinity of HSV may also explain why similar development of NMDAR encephalitis has not been documented following other neurological diseases, such as stroke or bacterial meningitis, where there is neuronal damage but involvement of the limbic system is uncommon.

Treatment

No data exists on the prevention of development of NMDAR encephalitis following HSVE, but as understanding for the underlying process advances, opportunity arises for potential therapy. The benefit of immunotherapy in patients who have developed NMDAR encephalitis following HSVE has been reported with both first-line treatment with corticosteroids, intravenous immunoglobulin, or plasmapheresis and second-line therapy with rituximab or cyclophosphamide in those refractory to first-line therapies [15•, 20]. While the benefit of immunotherapy with corticosteroids in HSVE has been documented [31–33], there have been no large-scale prospective clinical trials (a planned trial in Europe failed to enroll enough patients). One retrospective study of 45 patients with HSVE found an association between poor outcome and those who did not receive corticosteroids [32]. Furthermore, the use of corticosteroids in patients with active HSVE has been shown to be clinically safe and does not increase overall viral load in smaller studies [33]. Improved outcomes with delayed administration of corticosteroids once patients are appropriately treated with acyclovir are attributed to an overall reduction of the inflammatory response and reduced brain edema. Studies examining the role of reduced secondary autoimmunity with concomitant used of steroids are lacking. It may be reasonable to consider corticosteroids as a possible preventive strategy in susceptible patients targeting the inflammatory environment permissive to the development of autoantibodies against neuronal tissue, but controlled-clinical trials are needed to study this further.

Conclusion

HSVE is often a monophasic disease, although rarely, relapsing disease can occur. Recent evidence demonstrates that many relapsing presentations that occur in patients whom received an appropriate course of antiviral therapy at the time of initial presentation have disease relapse due to the subsequent development of NMDAR autoantibodies leading to NMDAR encephalitis rather than an ongoing viral infection. Potential mechanisms for the development of post-HSVE autoimmune encephalitis include molecular mimicry or an immune response to unmasked antigen in the context of infection-induced cellular damage. Future studies are needed to address the possibility of shared epitopes between HSV and NMDAR, as well characterization of the immune and inflammatory environment within the HSV-infected microenvironment of the limbic system. A clinical trial of corticosteroid during the initial HSVE course for prevention of secondary development of NMDAR encephalitis would also be informative.

Compliance with Ethical Standards

Conflict of Interest Drs. Galli, Clardy, and Piquet declare no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1.• Armangue T, Leypoldt F, Dalmau J. Autoimmune encephalitis as differential diagnosis of infectious encephalitis. Curr Opin Neurol. 2014;27(3):361–8. **This article compares and contrasts the differences between infectious and autoimmune encephalitis including clinical findings, cerebrospinal fluid findings, and imaging findings, as well as treatment response. The authors also provide a literature review of autoimmune encephalitis and discuss the evidence of HSVE-inducing synaptic autoimmunity**.
2. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2010;17(8):999–e57.
3. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis. 2009;28(12):1421–9.
4. Chaudhuri A, Kennedy PG. Diagnosis and treatment of viral encephalitis. Postgrad Med J. 2002;78(924):575–83.
5. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012;54(7):899–904.
6. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain. 2010;133(9):2734–48.
7. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol. 2009;65(4):424–34.
8. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010;9(1):67–76.
9. Carvajal-González A, Leite MI, Waters P, Woodhall M, Coutinho E, Balint B, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. Brain. 2014;137(Pt 8):2178–92.
10. Linnoila JJ, Rosenfeld MR, Dalmau J. Neuronal surface antibody-mediated autoimmune encephalitis. Semin Neurol. 2014;34(4):458–66.
11. Lancaster E, Dalmau J. Neuronal autoantigens—pathogenesis, associated disorders and antibody testing. Nat Rev Neurol. 2012;8(7):380–90.
12. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12(2):157–65.
13. Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist. 2007;13(5):261–71.
14. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338:94–114.
15.• Armangue T, Leypoldt F, Málaga I, Raspall-Chaure M, Marti I, Nichter C, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol. 2014;75(2):317–23. **The authors prospectively identified five patients with relapsing neurological symptoms following HSVE with new development of NMDAR antibodies and response to immunotherapy. They also retrospectively reviewed the cerebrospinal fluid in 34 patients with HSV encephalitis (CSF obtained following initial encephalitis) and demonstrated antibodies in two patients against NMDAR, nine patients against unknown antigen, and one against both. This demonstrates an association between HSVE and the possible development of NMDAR antibodies in the setting of relapsing disease and a possible broader immunological response and development of multiple autoantibodies**.
16. Valencia I, Miles DK, Melvin J, Khurana D, Kothare S, Hardison H, et al. Relapse of herpes encephalitis after acyclovir therapy: report of two new cases and review of the literature. Neuropediatrics. 2004;35(6):371–6.
17. Sköldenberg B, Aurelius E, Hjalmarsson A, Sabri F, Forsgren M, Andersson B, et al. Incidence and pathogenesis of clinical relapse after herpes simplex encephalitis in adults. J Neurol. 2006;253(2):163–70.
18. Barthez MA, Billard C, Santini JJ, Ruchoux MM, Grangeponte MC. Relapse of herpes simplex encephalitis. Neuropediatrics. 1987;18(1):3–7.
19.• Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol. 2012;72(6):902–11. **This retrospective analysis of 44 patients with polymerase chain reaction proven herpes simplex encephalitis demonstrates the presence of a pathogenic NMDAR antibody targeting the NR1a subunit occurring in the setting of HSVE**.
20. Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-

clinical analysis and novel findings in a series of 20 patients. J Pediatr. 2013;162(4):850–6.e2.

21. Hacohen Y, Deiva K, Pettingill P, Waters P, Siddiqui A, Chretien P, et al. N-methyl-D-aspartate receptor antibodies in post-herpes simplex virus encephalitis neurological relapse. Mov Disord. 2014;29(1):90–6.

22.• Linnoila JJ, Binnicker MJ, Majed M, Klein CJ, McKeon A. CSF herpes virus and autoantibody profiles in the evaluation of encephalitis. Neurol Neuroimmunol Neuroinflamm. 2016;3(4):e245. **This study retrospectively reviews the cerebrospinal fluid of 100 patients with HSV-PCR-positive encephalitis finding multiple antibodies including NMDAR antibodies. CSF of 77 patients with autoimmune encephalitis was retrospectively reviewed with four patients found to have the presence of herpes viruses. Lastly, cases with history concerning for parainfectious encephalitis were assess with five patients noted to have biphasic courses with HSV detected during the first course and NMDAR antibodies detected during the second course. These findings add to the association between HSVE and the possible development of synaptic autoimmunity**.

23. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008;7(12):1091–8.

24. Leypoldt F, Titulaer MJ, Aguilar E, Walther J, Bönstrup M, Havemeister S, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. Neurology. 2013;81(18):1637–9.

25. Ang CW, Jacobs BC, Laman JD. The Guillain-Barré syndrome: a true case of molecular mimicry. Trends Immunol. 2004;25(2):61–6.

26. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. Nat Med. 2003;9(7):914–20.

27. Araujo AQ, Silva MT. The HTLV-1 neurological complex. Lancet Neurol. 2006;5(12):1068–76.

28. Mameli G, Cocco E, Frau J, Marrosu MG, Sechi LA. Epstein Barr virus and Mycobacterium avium subsp. paratuberculosis peptides are recognized in sera and cerebrospinal fluid of MS patients. Sci Rep. 2016;6:22401.

29. Pradhan S, Gupta RK, Singh MB, Mathur A. Biphasic illness pattern due to early relapse in Japanese-B virus encephalitis. J Neurol Sci. 2001;183(1):13–8.

30. Schäbitz WR, Rogalewski A, Hagemeister C, Bien CG. VZV brainstem encephalitis triggers NMDA receptor immunoreaction. Neurology. 2014;83(24):2309–11.

31. Ramos-Estebanez C, Lizarraga KJ, Merenda A. A systematic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy? Antivir Ther. 2014;19(2):133–9.

32. Kamei S, Sekizawa T, Shiota H, Mizutani T, Itoyama Y, Takasu T, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry. 2005;76(11):1544–9.

33. Meyding-Lamadé UK, Oberlinner C, Rau PR, Seyfer S, Heiland S, Sellner J, et al. Experimental herpes simplex virus encephalitis: a combination therapy of acyclovir and glucocorticoids reduces long-term magnetic resonance imaging abnormalities. J Neurovirol. 2003;9(1):118–25.